***Objection to the Disclosure***

The specification has been amended to correctly indicate that the Example starting at page 56 is Example 2, thereby obviating the rejection.

***Rejection of claims 1-36 under 35 U.S.C. § 112, first paragraph***

Claims 1-36 stand rejected under 35 U.S.C. § 112, first paragraph, because

> the specification, while being enabling for a method for inhibiting calcineurin/NF-AT mediated transcription *in vitro* using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively, does not reasonably provide enablement for methods of inhibiting calcineurin/NF-AT mediated transcription *in vivo*, for methods of inhibiting proliferation of hematopoietic cells *in vivo* or *in vitro*, or for treating graft-versus host disease in a patient using any mutated macrolide/macrolide binding protein combination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicants respectfully traverse the rejection.

It is the Examiner's position, that "the specification does not provide an enabling disclosure for inhibiting proliferation of hematopoietic cells *in vitro* or *in vivo*", because "the specification does not demonstrate a correlation between the inhibition of transcription observed in cells stimulated with phorbol ester and ionomycin and inhibition of cellular proliferation caused by any and all growth factors."

The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation". Nevertheless, all that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, scope of enablement must only bear a "reasonable correlation" to the scope of the claims. E.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As acknowledged by the Examiner, Applicants teach a method of inhibiting calcineurin/NF-AT mediated transcription *in vitro*. In fact, Applicants' working examples demonstrate that a mutated macrolide binding protein (MBP)/mutated complementary macrolide complex is capable of

binding to calcineurin and thereby inhibiting NF-AT dependent transcription of a target gene. Applicants respectfully submit that it was well known in the art at the time the invention was made that NF-AT regulates the transcription of various cytokines that are involved in cell proliferation and that this is the mechanism whereby, at least in part, immunosuppressants such as cyclosporin A and FK506 function. "Cyclosporin A bocks IL-2 production from lymphocytes and thereby inhibits IL-2 induced cell proliferation" from "*Cellular and Molecular Immunology*" Abul Abbas, A. Lichtman, and J. Pober, Second Ed., Saunders eds., at page 349, left column. Regarding FK506, see, e.g., Mori et al. (cited by the Examiner) which states that "[d]ue to the lack of NF-AT induction, IL-2 synthesis is abrogated by FK506." It was also well known in the art that at least some of the NF-AT dependent genes are involved in cell proliferation, most notably the IL-2 gene. In fact, IL-2 was originally called "T cell growth factor", and as indicated in Abul Abass et al., supra at page 251, bottom of right column, "IL-2 [] is the principal cytokine responsible for progression of T lymphocytes from the G1 to S phase of the cell cycle." Thus, a person of skill in the art would readily have anticipated, at the time the invention was filed, that an inhibition of NF-AT mediated gene transcription in a cell, such as by cyclosporin A or FK506, would result in inhibition of proliferation of the cell.

The Examiner relied on Mori et al. as teaching that FK506 does not inhibit proliferation of T cell clones mediated by the experimental addition of IL-2. Applicants acknowledge that IL-2 stimulates T cell proliferation. However, applicants respectfully submit that the experiment is not relevant or dispositive here since it is known that FK506 inhibits the production of IL-2. Whether or not FK506 also inhibits the activity of IL-2 is not necessarily germane here. FK506-FKBP complex inhibits the activity of calcineurin which is required for activation of NF-AT (p. 3659, right column). Due to the lack of NF-AT induction, IL-2 synthesis is abrogated by FK506 (page 3659, right column). It is at least through this IL-2 synthesis abrogation that FK506 exerts its anti-proliferative effect on T cells. Simply, FK506 inhibits T cell proliferation at least in part by inhibiting IL-2 production.

The Examiner states that "the specification does not provide guidance as to the level of transcriptional inhibition necessary to inhibit proliferation" and that "while the specification's transcriptional assays demonstrate the concentration of macrolide analog required to achieve 50% or greater inhibition of transcription in cells expressing an unknown level of mutated MBP, they do not provide guidance as to the level of mutated MBP expression required for the successful inhibition of transcription or proliferation."

However, Applicants note that enablement does not require optimization of proof of efficacy of the sort required by the FDA, nor is enablement precluded if some experimentation is necessary. See In re Colianni, 561 F 2d at 224, 195 USPQ at 153. In this case, the Examiner has not set forth a rationale for any particular criticality for the expression level parameter. In fact, the level of mutated MBP expression required or desired for the claimed invention is not a specific value, but can vary depending on factors such as choice of MBP, macrolide, etc. which are within the discretion of the practitioner. Approaches for adjusting expression level are (and were) well known, and include adjusting the amount of vector, choice of promoter, etc.

With respect to the issues raised by the Examiner relating to *in vivo* transduction of hematopoietic cells, the claim amendments are believed to render moot any such concerns. Applicants reiterate that these amendments are being made for expediency, and that they reserve the right to prosecute claims to subject matter as originally filed.

The Examiner further indicates that "[t]he specification does not provide an enabling disclosure for the selective inhibition of proliferation of transplanted hematopoietic cells or the treatment of graft-versus-host disease in an individual comprising transplanting hematopoietic cells of which a sub-population express a mutated MBP, followed by administration of a complementary macrolide analog" since "the specification does not provide guidance as to the percentage of T cells which need to be transfected, or the level of expression of the mutated MBP in the donor T cells that is required to treat GVHD." Again, the Examiner has not provided a rationale for the assumed criticality of these parameters. Applicants' examples demonstrate the proof of principle in cell cultures, and no specific reason to doubt the operability of the invention *in vivo* has been presented.

The Examiner contends that the percentage of donor T cells expressing the mutated MBP would be critical to the success of the instant invention, and in absence of guidance from the specification, the skilled artisan would not predict that GVDH could be treated when expression of the mutated MBP was transient and where the percentage of donor T cells expressing the mutated MBP was less than 100%."

Applicants respectfully submit that the claims, as newly amended, are drawn to a method for reducing GVHD, rendering this rejection moot.

In view of all of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

***Rejection of claim 31 under 35 U.S.C. § 112, second paragraph***

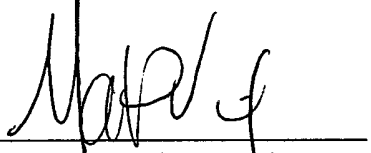
The Examiner rejected claim 31 under 35 U.S.C. § 112, second paragraph, for reciting "at least one sub-population of hematopoietic cells", contending that it is unclear what the characteristics of the subpopulation of cells might be and what percentage of these cells need to be transduced in order for graft-versus host disease to be treated. The claims was also rejected for not relating the inhibition of proliferation of a sub-population of hematopoietic cells with the treatment of GVHD.

Claim 31 has been amended, thereby obviating the rejection. Withdrawal of the rejection is respectfully requested.

***Conclusion***

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Agent would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

Respectfully submitted,
FOLEY, HOAG & ELIOT LLP



Matthew P. Vincent, Ph.D.
Registration No. 36,709
Attorney for Applicants

Patent Group
FOLEY, HOAG & ELIOT LLP
One Post Office Square
Boston, MA 02109
(617) 832-1000
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